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Chapter 1: Gout and Hyperuricemia

INTRODUCTION

- *Gout* involves an inflammatory response to precipitation of monosodium urate (MSU) crystals in both articular and nonarticular tissues.

CLINICAL PRESENTATION

- Elevated serum uric acid (hyperuricemia) is defined as serum supersaturated with MSU, exceeding its solubility limit (>6.8 mg/dL [404 µmol/L]).
- Urate crystal deposition in synovial fluid triggers inflammation, vasodilation, and chemotaxis of polymorphonuclear leukocytes.
- Acute gout attacks feature rapid onset of excruciating pain, erythema, warmth, and swelling. They are typically monoarticular, most often affecting the first metatarsophalangeal joint (podagra), followed by the insteps, ankles, heels, knees, wrists, fingers, and elbows. Attacks usually begin at night, waking the patient with intense pain. Affected joints are erythematous, warm, and swollen. Fever and leukocytosis are common. Without treatment, attacks last 3–14 days and resolve spontaneously.
- Acute attacks may occur spontaneously or be triggered by stress, trauma, alcohol, infection, surgery, rapid uric acid reduction from urate-lowering therapy, or drugs that raise serum uric acid levels.
- Uric acid nephrolithiasis occurs in ~10% of gout patients. Risk factors include high urinary uric acid excretion, acidic urine (pH <6), and concentrated urine.
- In acute uric acid nephropathy, kidney injury results from urine flow obstruction due to massive uric acid crystal precipitation in collecting ducts and ureters. Chronic urate nephropathy arises from prolonged urate crystal deposition in the renal parenchyma.
- Tophi (urate deposits) are rare and typically a late complication of hyperuricemia. Common sites include the bases of fingers, olecranon bursae, ulnar forearm, Achilles tendon, knees, wrists, and hands.

DIAGNOSIS

- Definitive diagnosis requires synovial fluid aspiration from the affected joint and identification of intracellular MSU monohydrate crystals in synovial fluid leukocytes.
- If aspiration is not feasible, a presumptive diagnosis relies on characteristic signs and symptoms and response to treatment.

TREATMENT

- Goals of Treatment: Terminate the acute attack, prevent recurrent attacks, and avoid complications from chronic urate crystal deposition in joints and tissues.

NONPHARMACOLOGIC THERAPY

- Local ice application is the most effective adjunctive therapy.
- Dietary supplements (eg, flaxseed, cherry, celery root) are not recommended due to unproven benefit.

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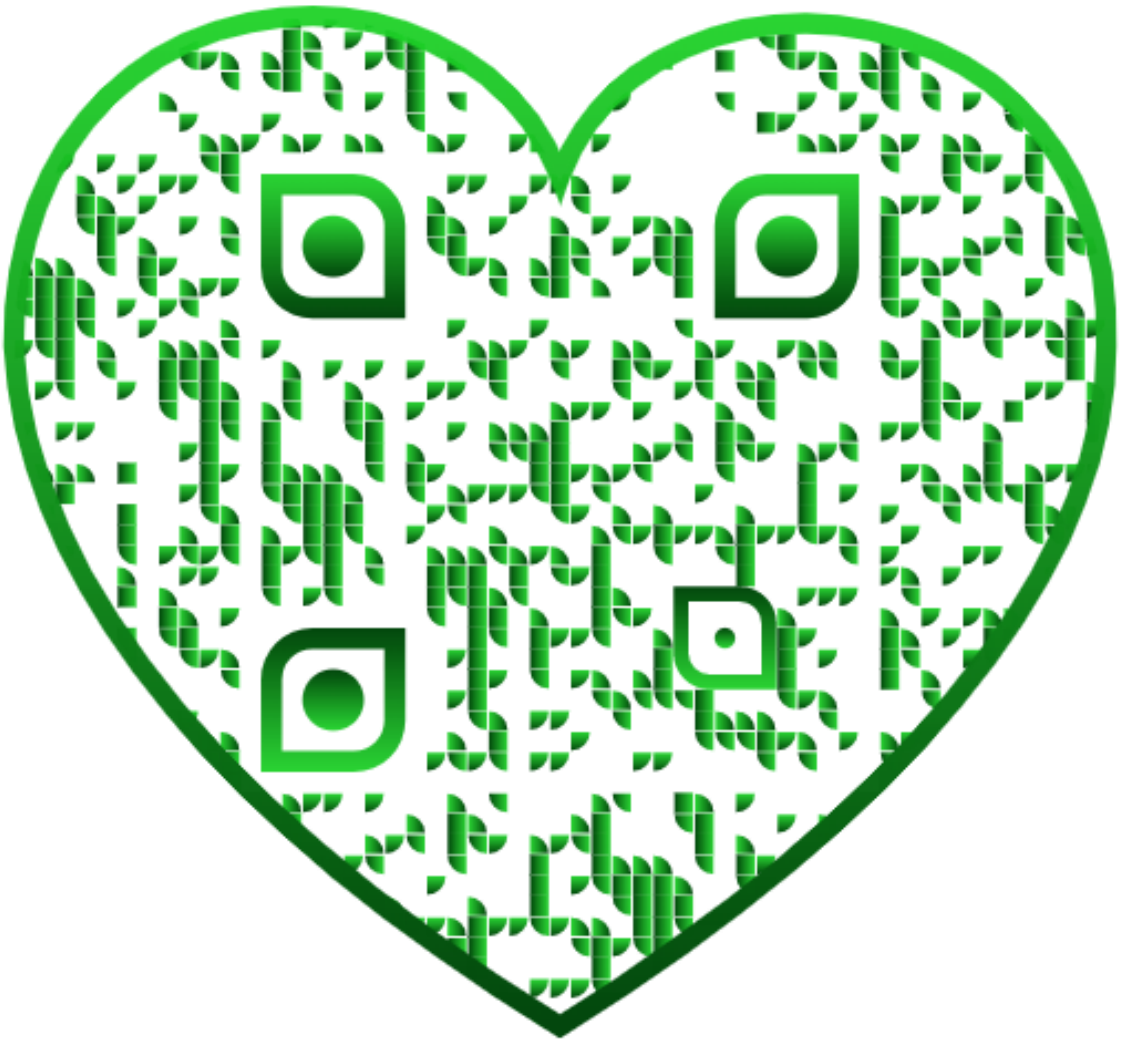

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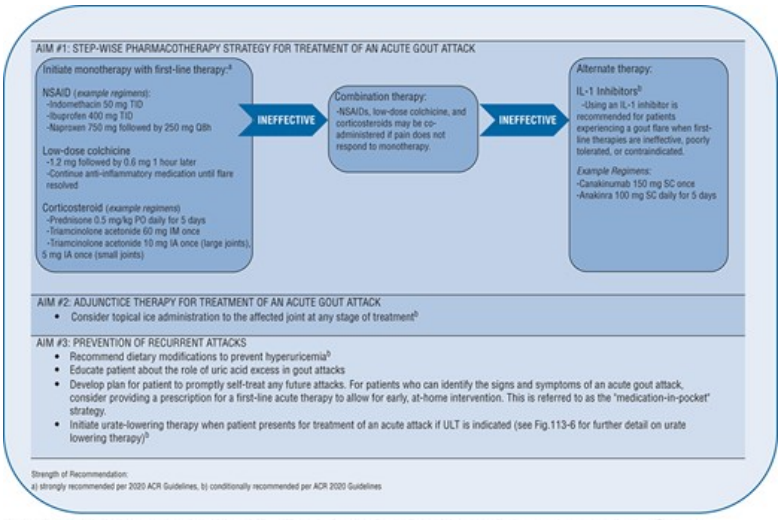
PHARMACOLOGIC THERAPY (FIG. 1-1)

- Most patients respond well to nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine. Treatment should start promptly after attack onset.

FIGURE 1-1

Comprehensive management of an acute gout attack. (IA, intra-articular; IM, intramuscular; PO, by mouth; SC, subcutaneous. Data from FitzGerald JD, Dalbeth N, Mikuls TB. 2020 American College of Rheumatology guideline for the management of gout. *Arthritis Care Res (Hoboken)* 2020;72:744–760.)


AIM #1: STEP-WISE PHARMACOTHERAPY STRATEGY FOR TREATMENT OF AN ACUTE GOUT ATTACK
Initiate monotherapy with first-line therapy:a
NSAID (example regimens):
-Indomethacin 50 mg TID
-Ibuprofen 400 mg TID
-Naproxen 750 mg followed by 250 mg QBh
Low-dose colchicine
-1.2 mg followed by 0.6 mg 1 hour later
-Continue anti-inflammatory medication until flare resolved
Corticosteroid (example regimens)
-Prednisone 0.5 mg/kg PO daily for 5 days
-Triamcinolone acetonide 60 mg IM once
-Triamcinolone acetonide 10 mg IA once (large joints), 5 mg IA once (small joints)
INEFFECTIVE
Combination therapy:
-NSAIDs, low-dose colchicine, and corticosteroids may be co-administered if pain does not respond to monotherapy.
INEFFECTIVE
Alternate therapy:
IL-1 Inhibitors[b]
-Using an IL-1 inhibitor is recommended for patients experiencing a gout flare when first-line therapies are ineffective, poorly tolerated, or contraindicated.
Example Regimens:
-Canakinumab 150 mg SC once
-Anakinra 100 mg SC daily for 3 days
AIM #2: ADJUNCTICE THERAPY FOR TREATMENT OF AN ACUTE GOUT ATTACK
Consider topical ice administration to the affected joint at any stage of treatment[b]
AIM #3: PREVENTION OF RECURRENT ATTACKS
Recommend dietary modifications to prevent hyperuricemia[b]
Educate patient about the role of uric acid excess in gout attacks
Develop plan for patient to promptly self-treat any future attacks. For patients who can identify the signs and symptoms of an acute gout attack, consider providing a prescription for a first-line acute therapy to allow for early, at-home intervention. This is referred to as the "medication-in-pocket" strategy.
Initiate urate-lowering therapy when patient presents for treatment of an acute attack if ULT is indicated (see Fig.113-6 for further detail on urate lowering therapy)[b]
Strength of Recommendation:
a) strongly recommended per 2020 ACR Guidelines, b) conditionally recommended per ACR 2020 Guidelines

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Lisa M. Holle, Cecily V. DiPiro: *DiPiro's Pharmacotherapy Handbook, 13th Edition*
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NSAIDs

- NSAIDs are highly effective with minimal toxicity when used short-term. Indomethacin, naproxen, and sulindac are Food and Drug Administration (FDA)–approved for gout, but other NSAIDs are also likely effective (**Table 1-1**).
- The most important determinant of therapeutic success is not which NSAID is chosen, but how quickly treatment is initiated. Since early intervention is more effective than delayed therapy, ensuring that patients have a plan to access treatment independently—known as the "medication-in-pocket" strategy—is a crucial component of optimized gout management.
- Begin treatment within 24 hours of symptom onset and continue until full resolution (typically 5–8 days). Tapering may be considered after resolution, especially if comorbidities like liver or kidney impairment increase the risk of adverse effects.
- Common side effects involve the gastrointestinal (GI) tract (gastritis, bleeding, perforation), kidneys (papillary necrosis, decreased glomerular filtration rate), cardiovascular system (elevated blood pressure, sodium and fluid retention), and central nervous system (cognitive changes, headache, dizziness).
- Selective COX-2 inhibitors (eg, celecoxib) may be alternatives for those intolerant to nonselective NSAIDs, though cardiovascular risks must be considered.

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TABLE 1-1

Dosage Regimens of Oral Nonsteroidal Anti-inflammatory Drugs for Treatment of Acute Gout

Generic Name	Initial Dose	Usual Range
Etodolac	300 mg twice daily	300–500 mg twice daily
Fenoprofen	400 mg three times daily	400–600 mg three to four times daily
Ibuprofen	400 mg three times daily	400–800 mg three to four times daily
Indomethacin	50 mg three times daily	50 mg three times daily initially until pain is tolerable; then, rapidly reduce to complete cessation
Ketoprofen	75 mg three times daily or 50 mg four times daily	50–75 mg three to four times daily
Naproxen	750 mg followed by 250 mg every 8 hours until the attack has subsided	—
Piroxicam	20 mg once daily or 10 mg twice daily	—
Sulindac	200 mg twice daily	150–200 mg twice daily for 7–10 days
Meloxicam	5 mg once daily	7.5–15 mg once daily
Celecoxib	800 mg followed by 400 mg on day 1; then, 400 mg twice daily for 1 week	—

Corticosteroids

- Corticosteroids are as effective as NSAIDs and can be used systemically or by intra-articular (IA) injection. Systemic therapy carries a hypothetical risk of rebound attack after withdrawal, so gradual tapering is often used.
- **Prednisone** or **prednisolone** dosing includes (1) 0.5 mg/kg daily for 5–10 days followed by abrupt stop or (2) 0.5 mg/kg daily for 2–5 days followed by tapering for 7–10 days.
- **Methylprednisolone dose pack** is a 6-day regimen, starting at 24 mg on day 1 and decreasing by 4 mg daily, that may be considered.
- **Triamcinolone acetonide** 20–40 mg IA can be used if gout affects one to two joints; doses of 10–40 mg IA for large joints and 5–20 mg IA for small joints are recommended. IA corticosteroids should be combined with an oral NSAID, colchicine, or corticosteroid therapy.
- **Methylprednisolone** IM injection followed by a short oral corticosteroid course is another option. IM corticosteroid monotherapy may be used for patients with multiple affected joints who cannot take oral drugs.
- Short-term corticosteroid use is generally well tolerated but caution is advised in diabetes, GI, bleeding, cardiovascular, and psychiatric disorders. Avoid long-term use due to risks of osteoporosis, adrenal suppression, cataracts, and muscle weakening.
- **Adrenocorticotropic hormone (corticotropin) gel** 25–40 USP units subcutaneously and repeated as needed has been used previously; its efficacy may match systemic corticosteroids, but first-line agents are preferred due to cost.

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Colchicine

- **Colchicine** effectively relieves acute gout attacks; when started within 24 hours of onset, about two-thirds of patients respond within hours.
- It causes dose-dependent GI side effects (nausea, vomiting, diarrhea). Non-GI effects include neutropenia and axonal neuromyopathy, worsened by other myopathic drugs (eg, statins) or impaired kidney function. Use cautiously with P-glycoprotein or strong CYP3A4 inhibitors (eg, clarithromycin, cyclosporine) due to increased colchicine levels and toxicity; dose reduction may be needed. Also, use cautiously in kidney or liver impairment.
- **Colcrys** is an FDA-approved colchicine tablet (0.6 mg). The recommended dose is 1.2 mg (two tablets) initially, then 0.6 mg 1 hour later. Though not FDA-approved, American College of Rheumatology (ACR) guidelines suggest 0.6 mg once or twice daily starting 12 hours after the initial dose, continuing until the attack resolves. Generic colchicine is also available.

MANAGING HYPERURICEMIA IN GOUT

- Recurrent gout attacks can be prevented by keeping uric acid low, but nonadherence to nonpharmacologic and pharmacologic treatments is common.

NONPHARMACOLOGIC THERAPY

- Patient education should cover gout's recurrent nature and the goals of lifestyle and dietary changes and medication.
- Promote weight loss through calorie restriction and exercise to improve renal urate excretion.
- Alcohol restriction is important, as higher intake increases gout attack risk.
- Limit high-fructose corn syrup and purine-rich foods (organ meats, some seafood) that raise uric acid. The DASH (Dietary Approaches to Stop Hypertension) diet may lower serum uric acid by ~1.0 mg/dL in compliant hyperuricemic patients. It emphasizes vegetables, fruits, whole grains, low-fat dairy, lean meats, beans, and nuts, while avoiding saturated fats and sweetened foods/beverages.
- Review medications for unnecessary drugs that raise uric acid. When possible, replace them with alternatives without this effect (eg, switch hydrochlorothiazide). Continue low-dose aspirin for cardiovascular prevention despite its uric acid–raising effects.

PHARMACOLOGIC THERAPY (FIG. 1-2)

- After the first acute gout attack, prophylactic pharmacotherapy is recommended if patients have two or more attacks yearly, even with normal or mildly elevated serum uric acid. Other indications include tophi and radiographic gout damage.
- Urate-lowering therapy can begin during an acute attack if anti-inflammatory prophylaxis is started.
- Use a stepwise approach to hyperuricemia (**Fig. 1-2**). Xanthine oxidase inhibitors are first-line; uricosurics are for those intolerant or contraindicated. In refractory cases, combine a xanthine oxidase inhibitor with a uricosuric agent (probenecid, losartan, or fenofibrate). Pegloticase may be used for severe cases unresponsive or intolerant to other therapies.
- The ACR guideline goal is to maintain serum uric acid below 6 mg/dL (357 µmol/L). Urate-lowering therapy should be prescribed long-term.

FIGURE 1-2

Algorithm for management of hyperuricemia in gout.

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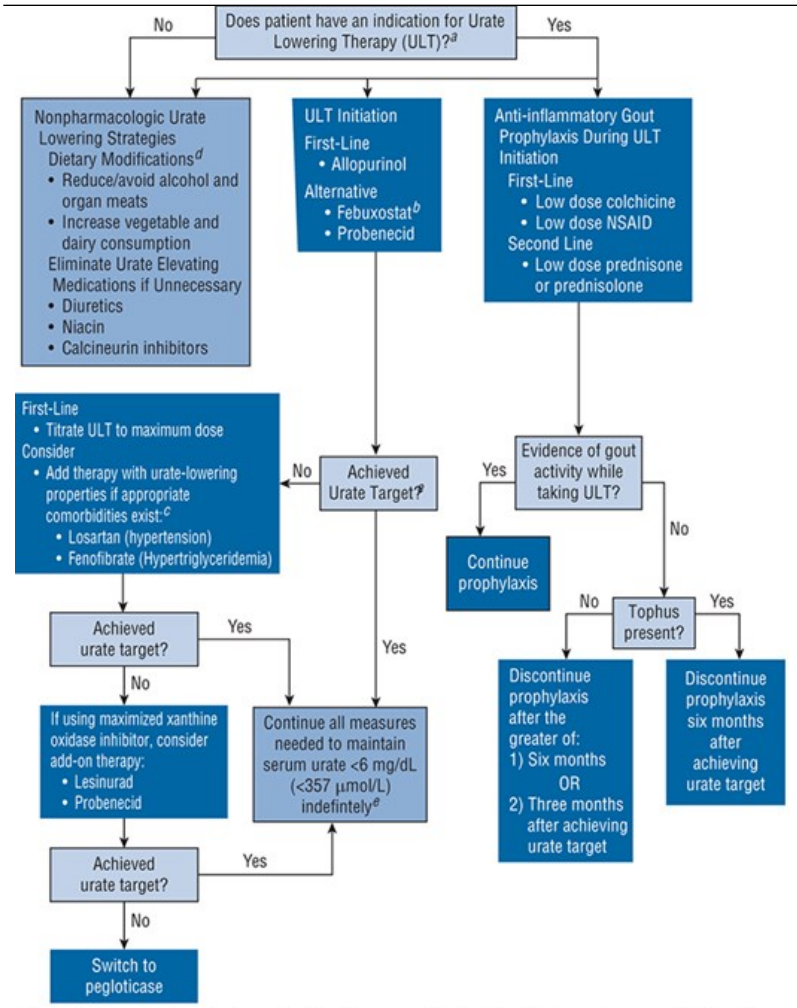

a) Indications for urate-lowering therapy include: 1) presence of tophus 2) ≥ 2 gout attacks per year 3) kidney disease 4) past urolithiasis. EULAR, but not ACR or ACP Guidelines, also recognize the following indications for ULT: 1) first diagnosis of gout at age < 40 years 2) uric acid > 8.0 mg/dL 3) high-risk comorbidities (hypertension, ischemic heart disease, hear failure)
b) Recognized as first line by ACR Guidelines but cardiovascular safety concerns have been reported since guideline publication
c) EULAR Guidelines also recognize calcium channel blockers and statins as add-on therapy for uric acid lowering when indicated for treatment of comorbidities
d) The effectiveness of dietary intervention in improving clinical outcomes is noted as an area of inconclusive evidence by 2017 ACP guidelines
e) Targeting and maintaining a specific urate level is noted as an area of inconclusive evidence by 2017 ACP guidelines

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Lisa M. Holle, Cecily V. DiPiro: *DiPiro's Pharmacotherapy Handbook, 13th Edition*
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Xanthine Oxidase Inhibitors

- Xanthine oxidase inhibitors lower uric acid by blocking conversion of hypoxanthine to xanthine and xanthine to uric acid. They are effective in both overproducers and underexcretors, making them the most prescribed agents for long-term gout prevention.
- **Allopurinol** reduces uric acid dose-dependently. ACR guidelines recommend starting ≤100 mg daily for normal kidney function and ≤50 mg/day for chronic kidney disease (CKD; stage 3–4 or worse) to avoid allopurinol hypersensitivity syndrome and prevent gout flares during initiation. Dose should be gradually titrated up to 800 mg/day based on serum uric acid levels.
- Mild side effects include rash, leukopenia, GI issues, headache, and urticaria. Rarely, allopurinol hypersensitivity syndrome occurs, marked by severe rash (toxic epidermal necrolysis, erythema multiforme), hepatitis, interstitial nephritis, and eosinophilia, with 20%–25% mortality. HLA-B*5801 allele increases risk.

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- **Febuxostat** (Uloric) also lowers uric acid dose-dependently, starting at 40 mg once daily, up to 80 mg daily. Side effects include nausea, arthralgias, and mild liver enzyme elevations. Trials showed increased all-cause and cardiovascular mortality versus allopurinol, so FDA labeling limits febuxostat to patients intolerant of allopurinol. Because urate mobilization can trigger flares, colchicine or NSAID prophylaxis is recommended for at least the first 8 weeks.

Uricosurics

- Uricosuric drugs increase renal clearance of uric acid by inhibiting its postsecretory proximal tubular reabsorption. Patients with a history of urolithiasis should avoid uricosurics. Start at a low dose to prevent excessive uricosuria and possible stone formation. Adequate urine flow and alkalinization during initial therapy may reduce stone risk. Uricosurics are generally not recommended in moderate to severe CKD.
- **Probenecid:** Start with 250 mg twice daily for 1–2 weeks, then 500 mg twice daily for 2 weeks. Increase by 500 mg every 1–2 weeks up to a maximum of 2 g/day or until control is achieved. Side effects include GI irritation, rash, hypersensitivity, gout flare, and urolithiasis. Maintain good hydration to lower stone risk.
- **Lesinurad** (Zurampic) inhibits urate transporter 1, increasing uric acid excretion. It is approved only in combination with a xanthine oxidase inhibitor for patients not reaching serum uric acid targets with monotherapy. Though FDA approved, it is not currently marketed because its clinical adoption was limited due to cost and concerns about renal side effects when used alone.

Pegloticase

- **Pegloticase** (Krystexxa) is a pegylated recombinant uricase that lowers serum uric acid by converting it to allantoin, a water-soluble compound. It is indicated for antihyperuricemic therapy in adults with gout refractory to conventional treatment.
- The dose is 8 mg by intravenous infusion over at least 2 hours every 2 weeks. Due to the risk of infusion-related allergic reactions, patients should be pretreated with antihistamines and corticosteroids. Pegloticase is significantly more expensive than first-line urate-lowering therapies.
- The optimal duration of pegloticase therapy is unknown. Antibodies may develop, reducing efficacy after several months.
- Due to these limitations, pegloticase should be reserved for patients with refractory gout who cannot tolerate or have failed other urate-lowering therapies.

Miscellaneous Urate-Lowering Agents

- **Fenofibrate** increases clearance of hypoxanthine and xanthine, reducing serum urate levels by 20%–30%. However, ACR guidelines advise against switching cholesterol-lowering agents to fenofibrate, as it is not preferred in current lipid management.
- **Losartan** inhibits renal tubular uric acid reabsorption and increases urinary excretion—effects not seen with other angiotensin II receptor blockers. It also alkalinizes urine, reducing stone risk. ACR guidelines recommend losartan as the preferred antihypertensive in gout patients when appropriate.

ANTI-INFLAMMATORY PROPHYLAXIS DURING INITIATION OF URATE-LOWERING THERAPY

- Starting urate-lowering therapy can trigger acute gout attacks due to remodeling of urate crystal deposits after rapid urate reduction. Prophylactic anti-inflammatory therapy is recommended to prevent flares.
- ACR guidelines strongly recommend low-dose oral colchicine (0.6 mg twice daily), low-dose NSAIDs (eg, naproxen 250 mg twice daily), or prednisone/prednisolone 10 mg daily during the first 3–6 months of therapy, and longer if flares continue. For patients on long-term NSAIDs, a proton pump inhibitor or other acid-suppressing therapy is advised to reduce gastric side effects.

EVALUATION OF THERAPEUTIC OUTCOMES

- Check serum uric acid levels in patients with suspected acute gout, especially if it is not the first attack and prophylaxis is being considered. Note

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that acute gout can occur even with normal uric acid levels.

- Monitor patients for relief of joint pain and for adverse effects and drug interactions. Pain from an initial gout attack typically begins improving within 8 hours of treatment, with full resolution of pain, erythema, and inflammation within 48–72 hours.
- For patients on urate-lowering therapy, assess kidney function, liver enzymes, complete blood count, and electrolytes at baseline and recheck every 6–12 months during long-term treatment.
- During urate-lowering titration, obtain serial serum uric acid levels. Once the target is reached, monitor levels every 6–12 months.
- Due to high comorbidity rates in gout (eg, diabetes, CKD, hypertension, obesity, coronary artery disease, heart failure, stroke), elevated uric acid or gout should prompt evaluation for these conditions and appropriate risk reduction. Also assess for reversible causes of hyperuricemia, such as medications, obesity, malignancy, or alcohol use.

See Chapter 118, Gout and Hyperuricemia, authored by Michelle A. Fravel and Michael E. Ernst, for a more detailed discussion of this topic.

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